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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,381	10/23/2003	Daniel D. Swartz	19226/2231 (R-5786)	8451

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Nixon Peabody LLP
Clinton Square
P.O. Box 31051
Rochester, NY 14603-1051

EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,381	SWARTZ ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-32,34-53,55 and 56* is/are rejected.

7)☒ Claim(s) *18,33 and 54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/15/04, 7/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application receives priority to Provisional Application No. 60/421,015, filed 10/23/2002.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor (Stelios T. Andreadis).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 16, 19, 24, 31-34, 39, 52 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 24 and 39 are vague and indefinite because they recite the phrase "1 to 4 $x10^6$ cells/ml" and it is not clear whether the Applicants intend $1x10^6$ cell/ml to 4 $x10^6$ cells/ml or 1 cell/ml to 4 $x10^6$ cells/ml.

Claims 16, 31 and 52 are vague and indefinite because they recite the phrase "specific organ cells" and the metes and bounds of the word "specific" are not clear. For example, are "specific organ cells" cells specific to an organ, such as hepatocytes, or

are "specific organ cells" those cells that are somehow distinguished from an organ with multiple cell types, such as endothelial cells?

Claim 32 is vague and indefinite because it recites the phrase "wherein the gelled fibrin mixture contains a porous scaffold" and it is not clear how a gelled mixture *contains* a scaffold.

Claims 19, 34 and 55 are vague and indefinite because they recite the phrase "wherein the porous scaffold is polylactic-glycolic acid" and it is not clear how a scaffold is polylactic-glycolic acid. It is not clear if the scaffold is comprised of polylactic-glycolic acid or if the polylactic-glycolic acid is polymerized into a scaffold structure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 8, 11, 14-17, 20-22, 24-25 and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Weinberg (U.S. Patent No. 4,837,379).

Weinberg teaches a method to prepare blood vessel tissue equivalent by casting a mixture of fibrinogen and thrombin and a suspension of vascular smooth muscle cells in a cylinder with a central mandrel in McCoy's medium with serum. Weinberg teaches placement of Dacron mesh over the tissue equivalent after the mixture has contracted around the mandrel (see column 8, lines 36-55 and column 2, lines 65-67, in particular) which reads on producing a tissue engineered vascular vessel comprising molding a fibrin mixture comprising fibrinogen, thrombin and cells suitable for forming a vascular vessel, such as vascular smooth muscle cells, into a tubular shape and incubating the fibrin gel in a medium suitable for the growth of the cells under effective condition to produce a tissue engineered vascular vessel, in combination with a porous scaffold. The method also reads on molding in a tube with an inner mandrel. Weinberg teaches that the vascular smooth muscle cells were used at densities of 0.5 $x10^6$ cells /ml or 2.0 $x10^6$ cells/ml (see column 8, lines 49-50, in particular) which reads on the claimed method with the cells suitable for forming a vascular vessel in a mixture of about 1 to $4x10^6$ cells/ml. Weinberg teaches that fibroblasts can also be used in the mixture (see column 3, lines 65-67, for example). Weinberg teaches that protease inhibitors can be included in the fibrin-collagen mixture to protect it from degradation (see column 4, lines 5-8, for example). Weinberg discloses that growth factors may be added to the tissue equivalent construct (see column 4, lines 9-14, for example). Weinberg further teaches that a layer of adventitial fibroblasts are added to the outside of the Dacron sheathed-fibrin smooth muscle layer (see column 8, lines 51-58, for example), which reads on the claimed

method wherein the vessel has an outer surface to which organ specific cells such as adventitial fibroblasts are added during molding.

Claims 1, 3, 5-7, 11, 20-21, 23, 25-27, 35-36, 38, 40-43, 47 and 56 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 6,787,357 (Bowlin et al).

Bowlin et al teach the use of fibrin in forming engineered tissue. Bowlin et al teach a method to produce a three dimensional biological matrix of plasma-derived fibrin formed from fibrinogen mixed with thrombin and suspended cells which are cultured in a cell culture apparatus for continued growth (see column 3, lines 45-54, column 4, lines 4-16 and column 5 lines 40-45). Bowlin et al teach that the fibrin and cell matrix can be formed into a specifically shaped mold or extruded to form tubes of fibrin (see column 6, lines 5-33, for example), which reads on a method of producing a vascular vessel by providing a fibrin mixture comprising fibrinogen, thrombin and cell suitable for forming a vascular vessel and molding the mixture into a tubular shape and further incubating the tubular fibrin gel in a medium suitable for growth of the cells. Bowlin et al teach that growth factors and nutrient can be added to the culture to promote a specific type of growth (see column 8, lines 50-55, for example). Bowlin et al further teach that the degradation of the fibrin mixture can be controlled by the addition of fibrinolytic inhibitor such as aprotinin, aminocaproic acid or similar fibrinolytic inhibitors. Bowlin et al disclose that fibroblasts can be used preparation of tissues with the fibrin matrix (see column 7, lines 6-21, for example) which reads on the claimed method wherein the cells suitable for forming a vascular vessel are fibroblasts. Bowlin

et al also teach that engineered tissue using a patient's own cells and fibrin would be beneficial and that the engineered vessel can be immediately inserted into a recipient (see column 1, line 64-67 and column 8, lines 48-55, in particular), which reads on a method of producing a tissue engineered vascular vessel for a particular patient by providing a fibrin mixture comprising fibrinogen, thrombin and cells autologous to the patient and molding the mixture into a tubular shape, incubating the tubular fibrin gel in a medium suitable for growth of the cells and implanting the engineered vascular vessel.

Claims 1-3, 8-9, 11-15, 20-23, 28-30, 35, 37-38, 40, 44-45, 47-51, 56 are rejected under 35 U.S.C. 102(a) as being anticipated by Simpson et al (U.S. Patent Application Publication No. US 2002/0090725).

Simpson et al teach methods and compositions of electroprocessed collagen and extracellular matrix compounds such as fibrin (formed from fibrinogen and thrombin) combined with cells of any type shaped into a preselected mold (see paragraphs 0009, 0011-012, 0048 and 0064). Simpson et al teach a method to form a tubular matrix using a cylindrical mandrel to make a vascular graft for use *in vivo* (see paragraphs 0146-0147, 0178). Simpson et al teach that fibroblast and smooth muscle cells can be used in some embodiments (see paragraphs 0092) which reads on producing a tissue engineered vascular vessel comprising molding a fibrin mixture comprising fibrinogen, thrombin and cells suitable for forming a vascular vessel into a tubular shape and incubating the fibrin gel in a medium suitable for the growth of the cells under effective

conditions to produce a tissue engineered vascular vessel. Simpson et al teach that the engineered tissue can be placed into a culture to enhance cell growth or placed into a recipient (see paragraph 0123 and 0190, for example), which reads on incubating the fibrin gel having a tubular shape under conditions effective to produce a tissue engineered vascular vessel. Simpson et al teach that to make a vascular prosthesis smooth muscle cells can be combined with the tubular structures, as well as fibroblasts on the outside of the tube (see paragraph 0193, for example) which reads on cells suitable for forming a vascular vessel being vascular smooth muscle cells or fibroblasts. Simpson et al disclose that the inventive method can include the use of growth factors such as VEGF, bFGF, PDGF and KGF (see paragraph 0098, in particular), which reads on the medium suitable for growth comprising a growth additive such as VEGF, b-FGF, PDGF and KGF. Simpson et al teach an embodiment of a vascular graft in which the culture media was changed every two days (see paragraph 0332, for example), which reads on the claimed method comprising change the medium suitable for growth. Simpson et al claim an embodiment of a cylindrical construct in which fibroblast cells are seeded on an exterior surface of the outer wall and endothelial cells are seeded on an interior surface of the inner wall of the construct enclosing a lumen (see paragraph 0295 and claim 16) which reads on a tissue engineered vascular vessel wherein the vessel has an outer surface with cells that are fibroblasts, and wherein the vessel has an interior surface on which endothelial cells are present. Simpson et al further teach a method of making a tissue engineered vessel in which cells and matrix from a patient (autologous) can be used (see paragraph 0077, 0122, 0190, 0198 and 0218, for

example), which reads on a method of producing a tissue engineered vascular vessel for a particular patient comprising providing vessel forming fibrin mixtures and cells autologous to the patient, modeling the mixture into a tubular shape, incubating the tubular fibrin gel under conditions to produce a vascular vessel for a particular patient and implanting the vessel. Simpson et al teach that the fibrin or collagen-containing matrix can be sprayed on to a metal screen inside a cylinder of a bioreactor (see paragraph 0137 and figure 3, for example), which reads on a method of molding being carried out in a tube with an inner mandrel.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 9-13, 16-17, 19-28, 31-32, 34-35, 37-43, 45-49, 52-53, 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niklason et al (U.S. Patent No. 6,537,567, filed 7/2/1998) in view of Grassl et al (June 2002, of record).

Applicants claim a tissue engineered vascular vessel and a method of making said vessel by molding a fibrin mixture comprising fibrinogen, thrombin and cells suitable for forming a vascular vessel into a tubular shape and incubating the tubular fibrin gel in a medium suitable for growth of cells under conditions effective to produce a tissue engineered vascular vessel.

Niklason et al teach a method to form tubular vascular constructs by using a porous substrate such as poly (lactic-co-glycolic) acid polymers in a tubular or cylindrical shape, with an inner and outer surface wherein the inner surface comprises a lumen to mold collagen (see column 2, lines 21-35, column 10, lines 12-15 and 45-56, column 11, lines 25-30 and 56-62 and collagen 12, lines 16-30 for example). Niklason et al teach that the construct can be seeded with cells, such as arterial fibroblasts, smooth muscle cells and endothelial cells seeded on the inner surface (see column 14, lines 19-29, column 15, lines 50-55 and column 16, lines 9-35). Niklason et al teach that smooth muscle cells are added to the construct at a concentration of ~ $1x\ 10^4$ to $5x10^7$ cells/ml (see column 30, lines 42-52, in particular). Niklason et al also teach that the cell growth medium can include b-FGF, VEGF or PDGF, and if the medium contains Vitamin C, may be replenished daily. Niklason et al teach that the tubular engineered construct is subjected to a pulsatile stretch to enhance the orientation of the smooth muscle cells around the lumen by a cyclic pulse rate of ~60-90/min (see column 20, lines 24-60). Niklason et al disclose that cells for use in the construct are preferably obtained from a live donor and harvested from the intended host especially for a construct for implantation into a living host (see column 16, lines 35-60, in particular).

Niklason et al does not teach that the tissue engineered vascular vessel is molded from a fibrin mixture comprising fibrinogen and thrombin.

Grassl et al teach fibrin as an alternative to collagen in artificial tissue constructs. Grassl et al teach that some cells, including aortic smooth muscle cells, exhibit only low amounts of extracellular matrix synthesis when embedded in collagen gels (see page

607, right column, 2nd paragraph). Grassl et al teach that cells synthesize more extracellular matrix components when embedded in fibrin, which has a pronounced effect on the mechanical properties of the gel (see page 608, left column, 2nd paragraph, for example). Grassl et al further teach that fibrin is formed from fibrinogen cleaved by thrombin and is susceptible to fibrinolysis unless a protease inhibitor such as epsilon (ε)- aminocaproic acid or aprotinin is included in the fibrin gel (see page 608, left column, 1st paragraph). Grassl et al teach that fibroblasts in fibrin gel tubes with a mandrel placed through the lumen produce tubular constructs with strong circumferential alignment of the cells.

It would have been obvious to one of ordinary skill in the art to combine the findings of Grassl et al with the method of Niklason et al to produce a fibrin-based tissue engineered vascular construct, because Niklason et al teach that various proteinaceous polymers can be used for tissue engineering methods, and Grassl et al teach improved mechanical properties of fibrin-based constructs when protease inhibitors are included. The motivation to do so would be the benefit suggested by Grassl et al and Niklason et al of having a vascular construct with better circumferential alignment of the seeded cells, more extracellular matrix produced by those cells and therefore, improved stability and mechanical properties for a vascular construct for implant into a patient. There is reasonable expectation of success in using a fibrin mixture in the vascular construct of Niklason et al because this has worked previously in the cited references.

Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary

skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

Claims 18, 33 and 54 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID GUZO
PRIMARY EXAMINER

Laura McGillem, PhD
3/27/2006